

In the Claims:

Please amend claims 1-41, 43, 45, and 46 as follows:

1. (Amended) A method of [generating] defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid sequence comprising generating a library of [nucleobase sequences *in silico* according to defined criteria] virtual compounds *in silico* according to defined criteria, and evaluating *in silico* the binding of said virtual compounds with said target nucleic acid according to defined criteria.
2. (Amended) A method of [generating] defining a set of [compounds] oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence comprising generating *in silico* a plurality of virtual oligonucleotides according to defined criteria, and evaluating *in silico* [a] the binding of said plurality of virtual oligonucleotides with said target nucleic acid according to defined criteria.
3. a2 (Amended) A method of [generating] defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid comprising, generating *in silico* a library of virtual compounds according to defined criteria wherein said virtual compounds modulate the expression of said target nucleic acid sequence, and robotically synthesizing [a plurality of defined oligonucleotide] synthetic compounds corresponding to at least some of said virtual compounds.
4. (Amended) A method of [generating] defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid comprising generating *in silico* virtual compounds according to defined criteria wherein said virtual compounds modulate the expression of said target nucleic acid sequence, synthesizing synthetic compounds corresponding to at least some of said virtual compounds, and robotically

assaying [a plurality of oligonucleotide] said synthetic compounds for one or more desired physical, chemical or biological properties.

5. (Amended) A method of [generating] defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid sequence comprising generating in silico a library of nucleobase sequences [*in silico*] according to defined criteria and evaluating *in silico* a plurality of virtual oligonucleotides having said nucleobase sequences according to defined criteria.

6. (Amended) A method of [generating] defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid sequence comprising evaluating *in silico* a plurality of virtual [oligonucleotides] compounds according to defined criteria and robotically synthesizing a plurality of synthetic [oligonucleotide] compounds corresponding to said plurality of virtual [oligonucleotides] compounds.

92 7. (Amended) A method of [generating] defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid sequence comprising evaluating *in silico* a plurality of virtual [oligonucleotides] compounds according to defined criteria and robotically assaying a plurality of synthetic [oligonucleotide] compounds corresponding to at least some of said virtual [oligonucleotides] compounds for one or more desired physical, chemical or biological properties.

8. (Amended) A method of [generating] defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid sequence comprising generating a library of nucleobase sequences *in silico* according to defined criteria and robotically synthesizing a plurality of synthetic [oligonucleotide] compounds having said nucleobase sequences.

9. (Amended) A method of [generating] defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid sequence comprising robotically synthesizing a plurality of synthetic [oligonucleotide] compounds and robotically assaying said plurality of synthetic [oligonucleotide] compounds for one or more desired physical, chemical or biological properties.

10. (Amended) A method of [generating] defining a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid sequence comprising generating a library of nucleobase sequences *in silico* according to defined criteria and robotically assaying a plurality of synthetic [oligonucleotide] compounds having at least some of said nucleobase sequences for one or more desired physical, chemical or biological properties.

92 11. (Amended) A method of generating a set of [compounds] oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence, comprising the steps of:

- (a) generating a library of nucleobase sequences *in silico* according to defined criteria;
- (b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of (a) according to defined criteria; and
- (c) robotically synthesizing a plurality of synthetic oligonucleotides [oligonucleotide compounds] corresponding to at least some of said virtual oligonucleotides.

12. (Amended) A method of generating a set of [compounds] oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence, comprising the steps of:

- (a) generating a library of nucleobase sequences *in silico* according to defined criteria;

(b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of (a) according to defined criteria; and

(c) robotically assaying a plurality of synthetic oligonucleotides [oligonucleotide compounds] corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties.

13. (Amended) A method of generating a set of [compounds] oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence, comprising the steps of:

(a) generating a library of nucleobase sequences *in silico* according to defined criteria;

(b) robotically synthesizing a plurality of synthetic oligonucleotides [oligonucleotide compounds] having at least some of said nucleobase sequences; and

(c) robotically assaying [a] said plurality of synthetic oligonucleotides [oligonucleotide compounds] for one or more desired physical, chemical or biological properties.

92 14. (Amended) A method of generating a set of [compounds] oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence, comprising the steps of:

(a) evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria;

(b) robotically synthesizing a plurality of synthetic oligonucleotides [oligonucleotide compounds] corresponding to at least some of said virtual oligonucleotides; and

(c) robotically assaying [a] said plurality of synthetic oligonucleotides [oligonucleotide compounds] for one or more desired physical, chemical or biological properties.

15. (Amended) A method of generating a set of [compounds] oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence, comprising the steps of:

- (a) generating a library of nucleobase sequences *in silico* according to defined criteria;
- (b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of (a) according to defined criteria;
- (c) robotically synthesizing a plurality of synthetic oligonucleotides [oligonucleotide compounds] corresponding to at least some of said virtual oligonucleotides; and
- (d) robotically assaying [a] said plurality of synthetic oligonucleotides [oligonucleotide compounds] for one or more desired physical, chemical or biological properties.

92 16. (Amended) A method of generating a set of [compounds] oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence, comprising the steps of:

- (a) generating a library of nucleobase sequences *in silico* according to defined criteria;
- (b) choosing an oligonucleotide chemistry;
- (c) robotically synthesizing a set of synthetic oligonucleotides [oligonucleotide compounds] having said nucleobase sequences of step (a) and said oligonucleotide chemistry of step (b);
- (d) robotically assaying said set of synthetic oligonucleotides [oligonucleotide compounds] of step (c) for a physical, chemical or biological activity; and
- (e) selecting a subset of said set of synthetic oligonucleotides [oligonucleotide compounds] of step (c) having a desired level of physical, chemical or biological activity in order to generate said set of compounds.

17. (Amended) A method of generating a set of [compounds] oligonucleotides that modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence, comprising the steps of:

- (a) generating a library of nucleobase sequences *in silico* according to defined criteria;
- (b) choosing an oligonucleotide chemistry;
- (c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of (a) and the oligonucleotide chemistry of (b) according to defined criteria, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;
- (d) robotically synthesizing a set of synthetic oligonucleotides [oligonucleotide compounds] having said preferred nucleobase sequences of step (c) and said oligonucleotide chemistry of step (b);
- (e) robotically assaying said set of synthetic oligonucleotides [oligonucleotide compounds] of step (d) for a physical, chemical or biological activity; and
- 92 (f) selecting a subset of said set of synthetic oligonucleotides [oligonucleotide compounds] of step (d) having a desired level of physical, chemical or biological activity in order to generate said set of [compounds] oligonucleotides.

18. (Amended) The method of claim [4] 12, wherein said step of robotically assaying said plurality of synthetic oligonucleotides [oligonucleotide compounds] is performed by computer-controlled real-time polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

19. (Amended) The method of claim [1] 11, wherein said target nucleic acid sequence is that of a genomic DNA, a cDNA, a product of a polymerase chain reaction, an expressed sequence tag, an mRNA or a structural RNA.

20. (Amended) The method of claim [1] 11, wherein said target nucleic acid sequence is a human nucleic acid.
21. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense [modulation] binding of an oligonucleotide to said nucleic acid sequences comprising generating a library of antisense nucleobase sequences *in silico* according to defined criteria.
22. (Amended) A method of [generating] identifying a set of compounds that modulate the expression of a target nucleic acid sequence via binding of said compounds with said target nucleic acid sequence comprising evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria.
23. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense [modulation] binding of an compound to said nucleic acid sequences comprising robotically synthesizing a plurality of synthetic antisense compounds.
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24. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense [modulation] binding of an compound to said nucleic acid sequences comprising robotically assaying a plurality of synthetic antisense compounds for one or more desired physical, chemical or biological properties.
25. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense [modulation] binding of an oligonucleotide to said nucleic acid sequences comprising generating *in silico* a library of nucleobase sequences [*in silico*] according to defined criteria and evaluating *in silico* a plurality of virtual oligonucleotides having said nucleobase sequences according to defined criteria.

26. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense [modulation] binding of an oligonucleotide to said nucleic acid sequences comprising evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria and robotically synthesizing a plurality of synthetic oligonucleotides [oligonucleotide compounds] corresponding to least some of said virtual oligonucleotides.

27. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense [modulation] binding of an oligonucleotide to said nucleic acid sequences comprising evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria and robotically assaying a plurality of synthetic oligonucleotides [oligonucleotide compounds] corresponding to least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties.

92 28. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense [modulation] binding of an oligonucleotide to said nucleic acid sequences comprising generating a library of nucleobase sequences *in silico* according to defined criteria and robotically synthesizing a plurality of synthetic oligonucleotides [oligonucleotide compounds] having said nucleobase sequences.

29. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense [modulation] binding of an oligonucleotide to said nucleic acid sequences comprising robotically synthesizing a plurality of synthetic oligonucleotides [oligonucleotide compounds] and robotically assaying said plurality of synthetic oligonucleotides [oligonucleotide compounds] for one or more desired physical, chemical or biological properties.

30. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense [modulation] binding of an oligonucleotide to said nucleic acid sequences comprising

generating a library of nucleobase sequences *in silico* according to defined criteria and robotically assaying a plurality of synthetic oligonucleotides [oligonucleotide compounds] having said nucleobase sequences for one or more desired physical, chemical or biological properties.

31. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense [modulation] binding of an oligonucleotide to said nucleic acid sequences comprising the steps of:

- (a) generating a library of nucleobase sequences *in silico* according to defined criteria;
- (b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of (a) according to defined criteria; and
- (c) robotically synthesizing a plurality of synthetic oligonucleotides [oligonucleotide compounds] corresponding to at least some of said virtual oligonucleotides.

52 32. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense [modulation] binding of an oligonucleotide to said nucleic acid sequences, comprising the steps of:

- (a) generating a library of nucleobase sequences *in silico* according to defined criteria;
- (b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of (a) according to defined criteria; and
- (c) robotically assaying a plurality of synthetic oligonucleotides [oligonucleotide compounds] corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties.

33. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense [modulation] binding of an oligonucleotide to said nucleic acid sequences, comprising the steps of:

- (a) generating a library of nucleobase sequences *in silico* according to defined criteria;

(b) robotically synthesizing a plurality of synthetic oligonucleotides [oligonucleotide compounds] having at least some of said nucleobase sequences; and

(c) robotically assaying [a] said plurality of synthetic oligonucleotides [oligonucleotide compounds] for one or more desired physical, chemical or biological properties.

34. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense [modulation] binding of an oligonucleotide to said nucleic acid sequences, comprising the steps of:

(a) evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria;

(b) robotically synthesizing a plurality of synthetic oligonucleotides [oligonucleotide compounds] corresponding to at least some of said virtual oligonucleotides; and

(c) robotically assaying [a] said plurality of synthetic oligonucleotides [oligonucleotide compounds] for one or more desired physical, chemical or biological properties.

52 35. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense [modulation] binding of an oligonucleotide to said nucleic acid sequences, comprising the steps of:

(a) generating a library of nucleobase sequences *in silico* according to defined criteria;

(b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of (a) according to defined criteria;

(c) robotically synthesizing a plurality of synthetic oligonucleotides [oligonucleotide compounds] corresponding to at least some of said plurality of virtual oligonucleotides; and

(d) robotically assaying [a] said plurality of synthetic oligonucleotides [oligonucleotide compounds] for one or more desired physical, chemical or biological properties.

36. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense [modulation] binding of an oligonucleotide to said nucleic acid sequences, comprising the steps of:

- (a) generating a library of nucleobase sequences *in silico* according to defined criteria;
- (b) choosing an oligonucleotide chemistry;
- (c) robotically synthesizing a set of synthetic oligonucleotides [oligonucleotide compounds] having said nucleobase sequences of step (a) and said oligonucleotide chemistry of step (b);
- (d) robotically assaying said set of synthetic oligonucleotides [oligonucleotide compounds] of step (c) for a physical, chemical or biological activity; and
- (e) selecting a subset of said set of synthetic oligonucleotides [oligonucleotide compounds] of step (c) having a desired level of physical, chemical or biological activity [in order to generate said set of compounds].

92 37. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense [modulation] binding of an oligonucleotide to said nucleic acid sequences, comprising the steps of:

- (a) generating a library of nucleobase sequences *in silico* according to defined criteria;
- (b) choosing an oligonucleotide chemistry;
- (c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of (a) according to defined criteria, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;
- (d) robotically synthesizing a set of synthetic oligonucleotides [oligonucleotide compounds] having said preferred nucleobase sequences of step (c) and said oligonucleotide chemistry of step (c);
- (e) robotically assaying said set of synthetic oligonucleotides [oligonucleotide compounds] of step (d) for a physical, chemical or biological activity; and

(f) selecting a subset of said set of oligonucleotides [oligonucleotide compounds] of step (d) having a desired level of physical, chemical or biological activity [in order to generate said set of compounds].

38. (Amended) The method of claim [24] 32, wherein said step of robotically assaying said plurality of [nucleic acid sequences] synthetic antisense oligonucleotides is performed by computer-controlled real-time polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

39. (Amended) The method of claim [21] 31, wherein said nucleic acid sequence is that of a genomic DNA, a cDNA, a product of a polymerase chain reaction, an expressed sequence tag, an mRNA or a structural RNA.

92 40. (Amended) The method of claim [21] 31, wherein said nucleic acid sequence is a human nucleic acid.

41. (Amended) A computer formatted medium comprising computer readable instructions for identifying [active] compounds that have one or more desired properties according to defined criteria and that bind to a genomic DNA, a cDNA, a product of a polymerase chain reaction, an expressed sequence tag, an mRNA or a structural RNA.

93 43. (Amended) A computer formatted medium comprising computer readable instructions for performing a method of identifying one or more nucleic acid sequences amenable to antisense [modulation] binding of a compound to said nucleic acid sequences.

54 45. (Amended) A computer formatted medium comprising one or more nucleic acid sequences amenable to antisense [modulation] binding of a compound to said nucleic acid sequences in computer readable form.

54 46. (Amended) A computer formatted medium comprising one or more nucleic acid sequences amenable to antisense [modulation] binding of a compound to said nucleic acid sequences in computer readable form, wherein said one or more nucleic acid sequences is identified according to the method of any one of claims 21[, 22 or 24]-40.

REMARKS

Claims 1-46 are pending in the present application.

Claims 1-41, 43, 45, and 46 have been amended herein.

The Office Action asserts at page 2 that the present application contains sequence disclosures for which errors in the computer readable form have been found. Applicants enclose herewith substitute pages 120-131 in order to comply with the Sequence Rules set forth in 37 CFR § 1.821-1.825. The enclosed substitute pages 120-131 contain the amended Sequence Listing, support for which can be found, for example, throughout the specification. No new matter has been added. In addition, please find enclosed herewith a Statement to Support Filing and Submission of DNA/Amino Acid Sequences in Accordance with 37 CFR §§ 1.821 through 1.825, and a computer readable form (CRF). In addition, the contents of the paper copy of the Sequence Listing and computer readable copy of the Sequence Listing, submitted in accordance with 37 CFR § 1.821(c) and (e), are the same.

The Examiner also asserts at page 4 of the Office Action that, although Form 1449 was received, no references were received. Applicants enclose a copy of the return card showing that the Patent Office did, in fact, receive copies of 217 references in connection with the IDS filed on August 31, 1999. Applicants will, however, endeavor to resubmit these references if they cannot be found at